REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the remarks which follow.

In this amendment, Applicants have amended claims 1, 34 – 36, 69 and 70. The amendments thereto are fully supported in the as-filed specification.

Claims 14 – 16, 21 – 25, 27 – 31, 56 – 68, 71 – 73, 82, 83 and 85 – 86 have been withdrawn. Applicants expressly reserve the right to file one or more continuing applications directed to the claimed subject matter.

The claims presently pending in the application are 1 – 13, 17 – 20, 34 – 45, 55, 69, 70, 74, 75 and 79 – 81. Claims 1 – 31, 34 – 45, 55 – 75 and 79 – 86 have been rejected under 35 USC § 103(a) as being unpatentable over Luo et al., in view of Sparer et al., Li et al., and Desai et al. This rejection is respectfully traversed.

In the outstanding Office Action of March 3, 2010, the Examiner persists in misinterpreting the results of the comparative tests provided and in overrating the teaching of Luo et al. so that once again the currently pending claims have been rejected for obviousness.

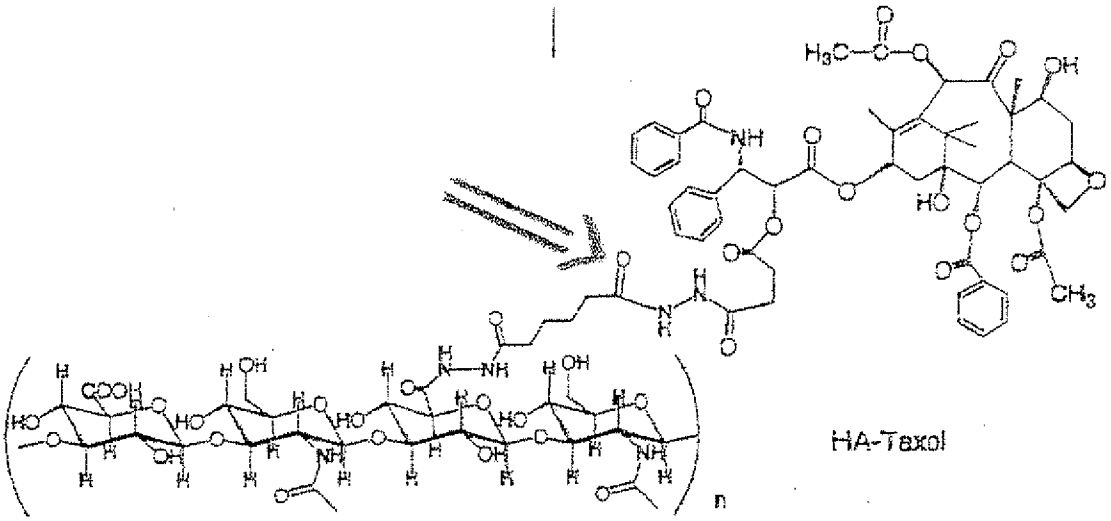
In order to accelerate the allowance of the subject Application, Applicants have determined to limit the scope of pending Claim 1 to a taxane covalently bonded to hyaluronic acid or to a hyaluronic acid derivative, wherein the covalent bond is formed by means of a spacer between hydroxyl groups of the taxane and carboxyl groups of the hyaluronic acid or hyaluronic acid derivative and the bond between the carboxylic groups of the hyaluronic acid or derivative thereof and the spacer is an ester bond, thus incorporating the subject matter of previously presented Claim 26, now cancelled, into Claim 1.

All of the previously presented claims which do not relate to the invention recited in claim 1 have been withdrawn from consideration.

In the outstanding Office Action (page 3, last paragraph, to page 4, first paragraph), the Examiner asserts that:

> Luo et al, drawn to bioconjugates, teach conjugates of hyaluronic acid wherein the carboxyl group of the hyaluronic acid is covalently bonded to a linker via an amide linkage to Taxol (Figure 2, page 756). Such conjugates showed selective toxicity towards human cancer cell lines that overexpress hyaluronic acid receptors like CD44 and RHAMM and the conjugates showed no toxicity (page 755, abstract, right column, last paragraph). In addition to this, conjugation of anticancer and antitumor drugs to biopolymers provides advantages in drug stabilization, solubilization, localization and controlled release (page 756, right column, below figure 4).
>
> In Figure 2 (page 756), Luo teaches the process for attachment of Taxol to hyaluronic acid wherein the carboxyl of the hyaluronic acid is attached to the spacer via an amide linkage on one end and the other end of the spacer is attached to the hydroxyl of the Taxol via an ester bond.

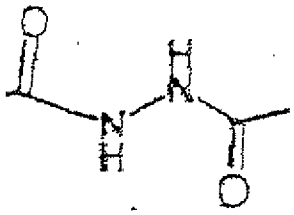
Applicants wish to point out that the compound Taxane-ADH-HA of Luo et al. does not involve an *amide bond*, but an **hydrazide** bond, as shown below (Figure 2 of Luo et al.):



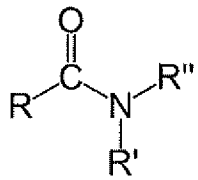
As clearly defined in the IUPAC nomenclature (see Enclosure 1), hydrazides in organic chemistry are a class of organic compounds sharing a common functional group

characterized by a nitrogen to nitrogen covalent bond with four (4) substituents with at least one of them being an acyl group.

In the case of Luo et al., there are two (2) acyl groups, thus giving a secondary hydrazide:



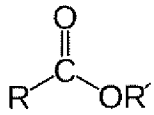
According to the IUPAC nomenclature (see Enclosure 2), amides are, indeed, derivatives of oxoacids in which an acidic hydroxy group has been replaced by an amino or substituted amino group:



Compounds having one, two or three acyl groups on a given nitrogen are generically included and may be designated as primary ($RCONH_2$), secondary (RCONHR) and tertiary amides ($RCONR_2$).

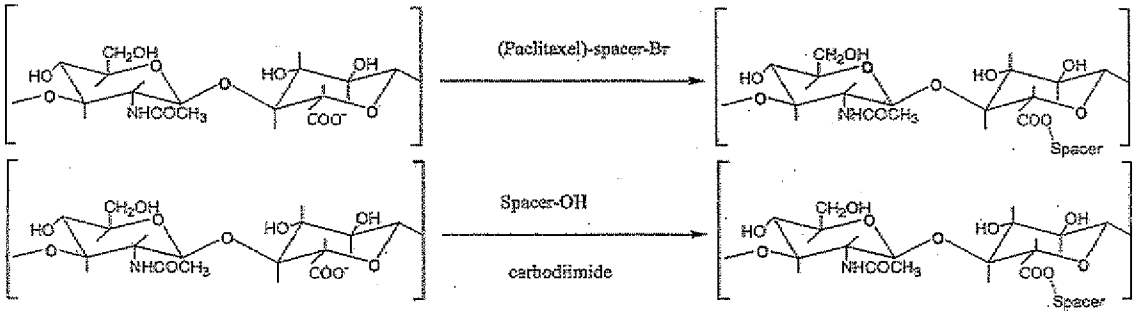
Therefore, the finding of the Examiner that Luo et al. disclose an amide bond is ***definitely incorrect.***

However, in the case of the claimed invention, the covalent bond is an ester bond between the spacer and the carboxyl groups of hyaluronic acid or a hyaluronic acid derivative. According to the IUPAC nomenclature (see Enclosure 3), esters are formed by condensing an acid RCOOH with an alcohol R'OH:



The claimed invention thus relates to the taxane covalently bound to hyaluronic acid or a hyaluronic acid derivative, wherein the covalent bond is an ester bond between the spacer and the carboxyl groups of hyaluronic acid or a hyaluronic acid derivative, as

clearly stated at page 8 (paragraph 0101) of the description and as shown in Schemes 11-12:



At page 4, second paragraph of the outstanding Office Action, the Examiner further affirms:

> However, the conjugate of Luo comprises hyaluronic acid conjugated to Taxol via a spacer that is a dihydrazide, which is excluded by the proviso in instant claim 1. But one of skill in the art reading Luo's teaching will realize the importance of the conjugate of Taxol and hyaluronic acid since Luo teaches that in addition to advantages with respect to drug stabilization, solubilization and controlled release of the conjugated drug, it has the advantage of hyaluronic acid as the carrier, which is immunoneutral, biocompatible and biodegradable and has been used as a vehicle and angiostatic agent in cancer therapy [emphasis added]

Later on, at page 9, first paragraph, the Examiner deduces:

> From this teaching it is evident that one of ordinary skill in the art will consider conjugating HA to Taxol. Since the hydrazide in Luo's conjugate (spacer) did not yield encouraging results, one of ordinary skill in the art would look for Taxol-HA conjugates with other spacers that may show better activity than free Taxol.
>
> One would also look for other types of linkages (based on the teaching of the secondary references. Sparer and Desai) that may be better than the ester linkage suggested by Luo.
>
> [emphasis added]

The Applicants strongly traverse this reasoning, as well as the derived conclusion, since it is based on a complete misinterpretation of the very teaching of Luo et al..

As a matter of fact, **Luo et al. give all their findings on the basis of results considered absolutely positive** for the conjugate HA-ADH-Taxol with respect to taxol as such, including the controlled release of the drug. Applicants demonstrated that these results **are, indeed, definitely negative and undesirable** under many aspects, therefore **the skilled person would have never considered Luo et al. as being technically reliable** and, accordingly, would never have had any interest in further investigating conjugates of HA and taxol.

Therefore, the reasoning that "one of skill in the art reading Luo's teaching will realize the importance of the conjugate of taxol and hyaluronic acid" cannot be maintained, since Luo et al. give a number of teachings being convinced that the results are positive and not negative, which in fact they are, ***despite*** *the fact the conjugate does not yield encouraging results*!

It should be kept in mind by the Examiner that the conjugate of Luo et al. has been demonstrated to be **fivefold less effective** than the free Taxol as such, therefore the expression "*non encouraging results*" is an euphemism! In the art, the result is definitely and unambiguously negative!

For these reasons and in consideration of all the arguments provided in Applicants' previous Responses, since the teachings in Luo et al. are the result of a misleading interpretation of the technical evidence, **the skilled person would have disregarded the whole document!**

As far as Sparer et al. are concerned, the Examiner acknowledged that this prior art document does not even concern taxol. Therefore, at the time the claimed invention was made, the skilled person would have had absolutely no reason to consider or to consult Sparer et al. in order to improve any aspect of the delivery of taxol.

Desai et al. (US patent allowed in 1997) refer to paclitaxel and docetaxel complexes with polyethylene glycol polymers, which is similar to the subsequent prior art document Li et al. (US patent allowed in 1999).

In this regard, at the time the claimed invention was made, one of ordinary skill in the art, having disregarded HA or an HA derivative for the reasons set forth above, would have, at most, considered the further investigation of taxol complexes like those described in Desai et al. or Li et al., i.e. involving polyethylene glycol polymers, thus unavoidably departing from the subject of the claimed invention.

In view of the above, the Applicants wonder how the Examiner could affirm, at the end of the Office Action (page 10, last sentence), that:

> Teaching, suggestion and motivation along with a reasonable expectation of success for the instant invention is seen in the prior art.

In other words, Applicants wonder how the conjugate of Luo et al., being fivefold less effective than the free Taxol as such, can be considered to be a suggestion and a motivation and provide reasonable expectation of success for **the conjugates of the claimed invention** showing **cytotoxicity** always greater than free Taxol, **in fact almost 150 times better than free Taxol!**

Consequently, the Applicants maintain that the Examiner came to his conclusions by an **ex post facto analysis**, i.e. by a **hindsight reconstruction,** having knowledge of the invention only from Applicants specification, considering that Luo et al. were

unambiguously unreliable, and none of the secondary references is able to remedy these deficiencies, since none of them involve technical teachings which are capable of overturning the "teaching away" of Luo et al. from the claimed invention.

In view of the foregoing, since the claims clearly distinguish over the prior art of record, the Examiner has clearly failed to establish a ***prima facie*** case of obviousness by a preponderance of the evidence, the rejection has been overcome and should be withdrawn.

The issue of a Notice of Allowance is solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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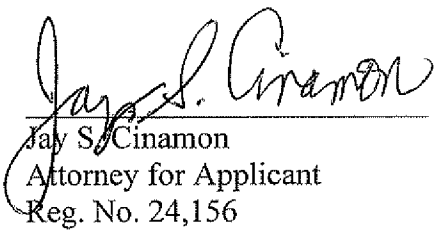
Attorneys for Applicant

By 
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